Rejection of Claims 73-75 and 109-112 under 35 U.S.C. §112, first paragraph

The Examiner has rejected claims 73-75 and 109-112 as lacking enablement. Specifically, the Examiner argues that the claims are only enabling for methods of providing a protein to a mammal, and not to methods of treating an animal since these claims may be construed to include gene therapy technology. With respect to claims 73-75, the rejection is rendered moot in view of the cancellation of these claims. Applicants respectfully traverse the rejection with respect to claims 109-112.

Applicants wish to point out to the Examiner that the subject matter of claim 112 falls squarely within the enabled subject matter iterated by the Examiner on page 2 of the Office Action. Thus, as to claim 112, Applicants respectfully request reconsideration and withdrawal of the rejection.

Claims 109-111 are enabled by the present specification. The Examiner has indicated that the data in the present application demonstrate that transgenic mice with a mutated COL1 A1 gene, when transfected with the marrow stromal cells (MSCs) of the present invention comprising a normal COL1 A1 gene, produce normal COL1 A1 protein. This is enablement. Applicants have shown that when MSCs carrying a normal copy of a gene which is defectively expressed in the recipient of the MSCs are transfected into an animal, the MSCs can and do correct expression of the defective gene. Animal models are regularly used to demonstrate therapeutic benefit of almost any treatment before use of such treatment in a human.

The Examiner contends that claims 109-111 read on gene therapy technology, and thinks that while the relative skill of those in the art of gene therapy is high, the area is unpredictable and *in vivo* and *ex vivo* gene therapy methods would require undue experimentation. The Examiner, applying the factors set forth in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), cites the following references in support of the rejection: Marshall (1995, Science, 269:1050), Verma (1997, Nature 389:239-242), Anderson (1998, Nature, 292:25-30), Moritz (1994, J. Clin. Invest., 93:1451-1457), Riddell (1996, Nature Medicine, 2:216-223), Onodera (1999, Acta Haemotologica 101:89-96), and Kohn (1995, Current Opinion in Pediatrics, 7:56-63). Applicants respectfully traverse.

The claimed cell and gene therapy methods are enabled by the specification as filed under the current law pursuant to 35 U.S.C. § 112, first paragraph.

It is well-settled that an Applicant need not have actually reduced the invention to practice prior to filing in order to satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph. MPEP §2164.02 (citing *Gould v Quigg*, 822 F.2d 1074 (Fed. Cir. 1987)). Indeed, the invention need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation (*in re Borkowski*, 422 F.2d 904, 908 (C.C.P.A. 1970), and "representative samples are not required by the statute and are not an end in themselves" *(in re Robins*, 429 F.2d 452, 456-457, 166 USPQ 552, 555 (CCPA 1970)). Thus, 35 U.S.C. § 112, first paragraph, enablement does not require any working examples.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. MPEP §2164.01 (citing *in re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976)). The fact that experimentation may be complex does not necessarily make it undue if the art typically engages in such experimentation. *Id.* Further, the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled in the art and already available to the public. MPEP §2164.05(a) (citing *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991)). Therefore, under current law, enablement does not require a working example and experimentation is allowed so long as it is not undue.

The Examiner cites a host of references for the notion that gene therapy was unpredictable at the time the invention was made. These references offer solutions to common problems encountered in gene therapy and offer data supporting use of gene therapy and its predictability. For example, Verma (1997, Nature 389:239-242) demonstrates continued expression of an exogenous nucleic acid encoding Factor IX at high levels for the life of a mouse, *i.e.*, two years (see page 240, middle column), and therapeutic expression of Factor IX in mice for over 6 months using adeno-associated viral vectors (AAV). Verma clearly demonstrates the high level of skill in the art where the pitfalls of gene therapy were known and that alternatives were also known as of September 1997. Thus, far from indicating that gene therapy cannot work, Verma demonstrates that gene therapy can and does work.

The Examiner also uses Marshall to bolster the argument that gene therapy is unpredictable, contending that Marshall informs us that the state of the art surrounding gene therapy in 1995 was "ambiguous" and "provided no evidence of therapeutic benefit". Applicants

have provided evidence of therapeutic benefit in an animal model, as have many others using gene therapy technology since 1995. Indeed, Marshall states that there were "several reports of convincing gene transfer and expression" during 1995 and earlier. In any event, Marshall cannot accurately represent the state of the art because the reference now contradicts what Applicants have demonstrated – a therapeutic benefit in an animal model using gene therapy techniques.

The Examiner also cites Moritz in support of his contention that gene therapy is an unpredictable art. Specifically, the Examiner states that Moritz demonstrates that although murine models have been successful in long-term gene expression, other larger animals such as dogs and primates have had limited success, mostly due to the low efficiency of infection of primitive hematopoietic stem cells. Applicants point out that the MSCs used for transfection in the present invention are mesenchymal in nature, and the cells on which transfected cells confer a therapeutic benefit are those tissues in closest proximity to the MSCs. The efficiency of infection of hematopoietic stem cells does not have any relevance to the present invention, and, in fact, distinguishes the present invention entirely from the prior art, as discussed more fully below. Further, Applicants note that the Carter reference, cited by the Examiner, demonstrates successful gene therapy methods in dogs. In any event, Moritz may demonstrate the state of the art with respect to hematopoietic stem cells, but the reference is not relevant to the present invention.

In addition, the specification as filed fully supports and enables claims 109-112 by presenting mouse model data. These data demonstrate that transfection into a mouse of MSCs having a normal copy of a gene that is defective in the mouse, provides the mouse with normal expression of the defective gene. Thus, Applicants have reduced their invention to practice in one animal, a mouse. It is well within the skill of the artisan to determine without undue experimentation, but with simple experimentation, routes of administration, dosage, etc., for practice of the invention in humans. The majority of experimentation to determine whether this method provides therapeutic benefit to an animal has been completed and has proved to be successful in an animal model. A practitioner, armed with the knowledge and information presented in the present specification, possesses the skill to apply this therapy to animals other than mouse, using the mouse model as a guide.

In sum, Applicants assert that the invention encompassed in claims 109-112 is fully enabled by the specification and does not require any undue experimentation. Therefore,

Applicants request reconsideration and withdrawal of the rejection to claims 109-112 under 35 U.S.C. §112, first paragraph.

Rejection of Claims 72-75 under 35 U.S.C. §112, second paragraph

The Examiner has rejected claims 72-75 as being indefinite as to whether Applicant intends to claim an animal comprising the container of the claims. Applicants have canceled these claims, thereby rendering the rejection moot.

Rejection of Claims 69-75, 99-101, 106-108, and 112 under 35 U.S.C. §103(a)

The Examiner has rejected claims 69-75, 99-101, 106-108, and 112 as being unpatentable in view of either Carter et al. (1992, Blood 79:356-364) or Cerami et al. (U.S. Pat. No. 5,846,796) in combination with any of Caplan (U.S. Pat. No. 5,197,985), Schinstine (U.S. Pat. No. 5,843,431), or Mardon (1987, Cell Tissue Res. 250:157-165). In the Examiner's view, Carter and Cerami teach a method of using isolated bone marrow stromal cells for implantation and providing a protein of interest to a cell in a mammal, wherein the cells are genetically modified to express the protein of interest. In addition, the Examiner contends that Cerami teaches implantation of isolated, genetically modified mesenchymal cells and a vector used with the mesenchymal cells having regulatory and screening elements. While, in the Examiner's view, Carter and Cerami do not teach use of a microcarrier, diffusion chamber or microcapsule to control release of isolated bone marrow stromal cells, the Examiner asserts that the state of the prior art as exemplified by Mardon, Caplan, and Schinstine, indeed teach that such delivery systems were routine and conventional. Thus, the Examiner believes that it would have been obvious to one skilled in the art to combine these references to arrive at the present invention. Applicants believe that the combination of either Carter or Cerami with any of the other references does not render these claims prima facie obvious. Thus, Applicants respectfully traverse this rejection for the following reasons.

The three-prong test which must be met for a reference or a combination of references to be prima facie obvious has not been satisfied here. The MPEP states that "to establish a prima facie case of obviousness...there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all of the claim limitations." MPEP 2142.

As more fully described below, these criteria have not been met here. First, neither Carter nor Cerami teach or suggest marrow stromal cells as disclosed by Applicants. The cells of Applicants' invention are defined in the specification bridging pages 4 and 5 as stromal cells, colony forming cells, marrow stromal cells, adherent cells, or MSCs (i.e., all these terms are synonymous with one another) and refer to the small fraction of cells in bone marrow that serve as stem-cell-like precursors of osteocytes, chondrocytes, and adipocytes, and can be isolated from bone marrow by their ability to adhere to plastic.

Carter discloses methods of gene transfer related to hematopoietic stem cells, or non-adherent cells, which are different cells than Applicants' stromal cells, which are adherent, mesenchymal precursor cells, described in the instant specification. The present specification makes clear that the cells of the present invention are adherent cells, which may differentiate into any of bone, cartilage, or adipose, and distinguishes these cells from non-adherent, hematopoietic precursor cells (see specification page 2, lines 3-5). Moreover, one of the advantages of Applicants' invention over the prior art is the ability to separate mesenchymal precursor cells (also referred to in the specification as marrow stromal cells) from hematopoietic precursor cells, which are clearly distinguished from the former. Therefore, Applicants submit that Carter does not teach or suggest marrow stromal cells which are mesenchymal stem cells.

Similarly, Cerami does not teach or suggest marrow stromal cells as characterized by Applicants. The cells in Cerami are also hematopoietic precursor cells. Applicants submit that Cerami is inapplicable for the same reasons as Carter, above. In addition, Applicants further contrast the present invention with that disclosed in Cerami because the cells in Cerami are isolated from peripheral blood and contain cell surface markers which are phenotypic for hematopoietic stem cells, and there is no showing of successful isolation of these cells from anything other than peripheral blood.

Moreover, while Cerami may disclose methods of isolating mesenchymal cells from peripheral blood, it does not teach using adherence of mesenchymal cells to plastic to isolate the cells. Rather, Cerami teaches using methods directed to antibodies to cell surface markers. Thus, Cerami does not teach or suggest Applicants' cells, which are defined as cells which adhere to plastic and isolated from bone marrow. In addition, Cerami does not teach or suggest that the mesenchymal cells disclosed in the reference can differentiate into chondrocytes, osteocytes, and adipocytes. Rather, the cells discussed in Cerami were indicated to be fibroblast-

like cells, and there was no teaching that these cells could differentiate at all. Thus, the feature of differentiation into chondrocytes, adipocytes, and osteocytes further distinguishes Applicants' invention from the prior art. Cerami's cells are therefore not Applicants' cells.

Neither Carter nor Cerami teaches that the MSCs be introduced into a syngeneically matched recipient.

In sum, neither reference teaches mesenchymal stem cells that can differentiate into chondrocytes, osteocytes, and adipocytes. Neither reference teaches isolating marrow stromal cells by adherence to plastic. Both of these criteria define the cells of the present invention. Thus, neither Carter nor Cerami teaches or suggests the present invention.

Applicants respectfully submit that combining Carter or Cerami with any one of Caplan, Schinstine, or Mardon does not correct the deficiencies of Carter or Cerami because none of these references combined with either Carter or Cerami teaches all elements of the present invention. Additionally, with respect to Caplan and Schinstine, the Examiner has not met his burden to prove a prima facie obviousness case as neither of these references was discussed as to its relevance in the present Office Action.

Caplan relates to isolation and differentiation of marrow-derived mesenchymal cells. Caplan discloses methods of adhering these cells to a container, which is then implanted into defective skeletal tissue, for example, so that the cells can proliferate into bone tissue.

The Mardon reference is similar in nature to the Caplan reference. Mardon does not teach or suggest the cells of Applicants' invention. Rather, Mardon teaches placing a mixture of marrow cells in a diffusion chamber for implantation in an animal. Thus, Mardon does not correct the deficiencies of either Carter or Cerami of teaching the Applicants' cells.

Neither Caplan nor Mardon discusses the concept of using the cells to correct expression of defective gene products in other cells. Carter, while discussing a gene therapy approach which confers a benefit on hematopoietic stem cells, does not discuss a gene therapy approach that confers a benefit on other types of cells. Thus, it would not have been obvious to one skilled in the art to combine these reference to arrive at the present invention.

Applicants contend that Schinstine is irrelevant to the present application because it deals with proliferation of cells within a bioartificial organ. Applicants are unclear as to how this reference relates to the present invention, except to demonstrate use of microcarriers as a known and accepted method to control or enhance delivery of a cell. In any event, Schinstine

does not overcome the deficiency of either Carter or Cerami to teach the MSCs of the present invention.

Based on the teachings of Flier and Beresford, the Examiner argues that there is a high likelihood of success that transfection of stromal cells with the vector comprising obesity factor DNA would be successful. Applicants point out here that the Examiner is using the teachings in Flier and Beresford, which demonstrate success with gene therapy methods, to support an argument of obviousness. Applicants remind the Examiner, as more fully described below, that references used to support a contention of obviousness must be enabling.

Applicants point out that the Examiner's rejections are contradictory. The Examiner first states that gene therapy is unpredictable in the rejection under 35 U.S.C. §112, first paragraph, but then uses the Carter, Beresford, and Flier references, which clearly indicate use of gene therapy techniques, in support of the argument that the combination of Carter with Flier and Beresford or any other reference above, is obvious, i.e., that gene therapy is obvious. The Examiner simply cannot have it both ways. It is settled law that a reference cannot render obvious a patent claim unless the reference enables the claim. See *In re Paulson*, 30 F.3d 1475, 1478, 31 USPQ 2d 1671, 1673 (Fed. Cir. 1994), wherein it is stated "a reference must be enabling and describe the applicant's claimed invention sufficiently to have placed it in possession of a person of ordinary skill in the field of the invention." Therefore, if the Examiner has supported his obviousness rejection with the Carter, Beresford, and Flier references, then Applicants draw the conclusion that these references are enabling references, and therefore enable the concept of gene therapy. On the flip side, Applicants assert that the Carter, Beresford, and Flier references must not enabling for gene therapy, in order to be in agreement with the Examiner's prior argument that the art of gene therapy is unpredictable and not enabled. In any event, one of these rejections must be withdrawn as each conflicts with the critical principles of the other.

In sum, Carter or Cerami combined with any of the above references does not render the invention obvious. In addition, Applicants request that either the obviousness rejection or the enablement rejection be reconsidered and withdrawn in view of the contradictory nature discussed by Applicants of the rejections. Applicants also request that the obviousness rejection be reconsidered and withdrawn in view of the foregoing arguments.

Summary

Applicants respectfully submit that each rejection of the Examiner to the claims of the present application has either been overcome or is now inapplicable, and that each of the claims 69-71 and 76-112 is in condition for allowance. Reconsideration and allowance of each of these claims are respectfully requested at the earliest possible date.

Respectfully submitted,

DARWIN PROCKOP, *ET AL.*

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(Date)

By: _____

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